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The Application of Microreactor Technology for the Synthesis of 1,2-Azoles

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Abstract:

We demonstrate the successful synthesis of an array of 1,2-azoles within a borosilicate glass microreactor whereby conversions in the range of 98−100% were obtained. In terms of large-scale production, this corresponds to 0.339 g day^{-1} per microreactor when employing reagent concentrations of 1.0 M.

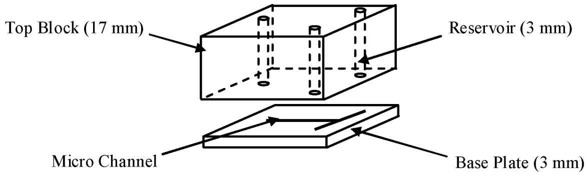

Figure 1. **Exploded view of a borosilicate glass microreactor.**

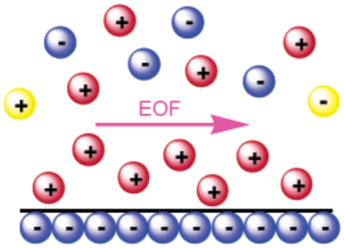

Figure 2. **Schematic illustrating the principle of electroosmotic flow.**

Introduction

Current production technology is based on the scale-up of successful lab-scale reactions in order to achieve large-scale production. This approach is however fundamentally flawed as at each stage of the scale-up, modifications made to the reactor vessel result in changes to the surface-to-volume ratio, which in turn have a profound effect on thermal and mass-transport properties of the reaction. As a result of these variations it is often necessary to re-optimise the process at each stage of the scale-up process. Consequently, the route from bench to production is both costly and time-consuming. It is therefore postulated that through the application of microreaction technology, the transfer of reactions from the laboratory to production will be both rapid and cost-effective.

The desire to miniaturise chemical synthesis has been driven by the need for greater process control as a means of increasing not only product purity but also reactor safety.[1] Using an approach referred to as scale-out or numbering-up,[2] a reaction is first optimised within the laboratory using a single microreactor, and to increase production volume, the number of reactors employed is simply increased. Consequently, a reaction is only optimised once, and all subsequent reactors are controlled using the same operating conditions. This approach is therefore both cost-effective, time saving, and flexible, enabling changes in production volume by simply increasing or decreasing the number of reactors employed. With these factors in mind, microreaction technology is of particular interest to the pharmaceutical industry, where long-term objectives include the desire to perform multiple functions such as synthesis, screening, detection, and biological evaluation within a single integrated device, resulting in an overall reduction in the time taken to discover new lead compounds and put them into production.

Microreactors. In the context of this paper, a microreactor is defined as a device containing a series of interconnecting channels formed in a planar substrate, with dimensions in the range 10−400 μm. Microreactors may be fabricated from glass, quartz, ceramics, polymers, and metals; however, due to its compatibility with organic solvents, high mechanical strength, temperature resistance, and optical transparency, borosilicate glass is the chosen substrate for the work described herein. As Figure 1 illustrates, the microreactor consists of a borosilicate glass base plate, containing an etched channel network, and a top block, containing the reagent reservoirs. Thermal bonding of the two layers affords a sealed microreactor, with typical dimensions in the range of 2.5 cm × 2.5 cm × 2.0 cm.[3]

To perform a reaction, reagents are brought together within the microchannel using a suitable pumping mechanism, reacted for a specified period of time, collected in the product reservoir, and analysed using a suitable technique. Although examples of pressure-driven systems have been reported within the literature, owing to its simplicity, the technique of electroosmotic flow (EOF) is frequently employed.[4] As Figure 2 illustrates, when an ionisable surface such as glass, quartz, or Teflon comes in contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid. A

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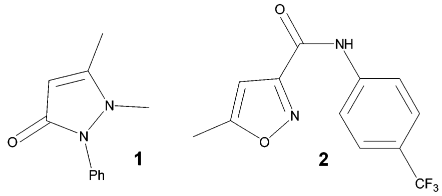

Figure 3. **Some heterocyclic compounds of pharmaceutical interest.**

proportion of the counterions are adsorbed onto the surface, resulting in the formation of an immobile layer, and the remaining positive ions form a transient double layer. Application of an electric field causes the double layer to move towards the negative electrode, inducing bulk flow within the microchannel.

With respect to fluidic manipulation, the use of EOF is advantageous as it is easy to use, requires no mechanical parts, enables reproducible pulse-free flow, and generates minimal backpressure. Therefore, with respect to scale-out, the technique is advantageous as multiple reagent streams can be controlled by a single power supply, maintaining the simplicity of the technique.

Advantages of Miniaturisation. As previously mentioned, the main advantage associated with the miniaturisation of chemical synthesis is the increased reactor control obtained, owing to the predictable thermal and mass transportation properties observed within the laminar flow environment.

In traditional large-scale reactor vessels, fluctuations in temperature are difficult to correct as any alterations made take time to have an effect on the system as a whole. In comparison, changes on the microscale are observed almost immediately. Along with increasing the rate of thermal mixing, decreasing the reactor dimensions results in an inherently high surface-to-volume ratio. Consequently, heat generated by exothermic reactions can be dissipated rapidly, reducing the likelihood of thermal runaway or hot-spot formation. As a result of the uniform reactor conditions obtained, a high degree of reaction control is observed.[5] Previous work has successfully demonstrated the ability to synthesise a range of compounds within an EOF-based microreactor including azo dyes, stilbene esters, peptides, 1,3-diketones and α,β-unsaturated carbonyl compounds, demonstrating both reduced reaction times and enhanced conversions compared to those observed in batch.[6]

1,2-Azole Synthesis. Heterocyclic compounds represent an important group of organic compounds, with many of them exhibiting significant biological activity, including anti-rheumatic agents such as antipyrine, **1**, and leflunomide, **2** (Arava) (Figure 3). To compare the use of a microreactor with traditional batch techniques, the reactions were initially performed in batch, enabling the products to be characterised.

Results and Discussion

As Scheme 1 illustrates, treatment of a 1,3-diketone with hydrazine monohydrate **3** (1.1 equivalents) in THF affords

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Scheme 1. **General reaction scheme illustrating the preparation of a series of 1,2-azoles**

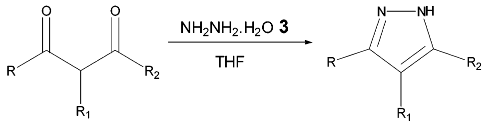

Table 1. **Summary of the conversions obtained for the batch-scale preparation of 1,2-azoles 4−8**

product no.	R−	R_1−	R_2−	conversion/%[a]
4	CH_3	H	CH_3	62
5	Ph	H	CH_3	63
6	$-(CH_2)_4-$		Ph	72
7	Ph	H	Ph	64
8	Ph	CH_3	CH_3	71

[a] Conversion based on GC−MS analysis of the crude reaction mixture after 1 h.

the respective 1,2-azoles **4**−**8** in excellent yield within a batch reaction. Using this methodology, a series of synthetic standards were prepared, representing synthetic targets for preparation within a microreactor. Analysis of the crude reaction mixture by GC−MS enabled the proportion of 1,2-azole to be determined with respect to residual 1,3-diketone i.e. percent conversion (Table 1).

Using the experimental setup illustrated in Figure 4, the preparation of 3,5-dimethyl-1*H*-pyrazole, **4**, was initially investigated by using the solvent system THF. A standard solution of 2,4-pentanedione **9** (40 μL, 0.1 M) in THF was placed in reservoir A, a solution of hydrazine monohydrate **3** (40 μL, 0.1 M) in THF was placed in reservoir B, and the reaction products were collected in THF at reservoir C. The reagents were manipulated within the device using the following applied fields, 292, 318, and 0 V cm^{-1} (A, B, and C respectively); analysis of the reaction products by GC−MS demonstrated 100% conversion of the 1,3-diketone **9** to 3,5-dimethyl-1*H*-pyrazole, **4**. The reaction was subsequently repeated using the solvent system DMF, whereby application of the following applied fields, 318, 318, and 0 V cm^{-1} again resulted in quantitative conversion to pyrazole **4**. The use of different applied fields compared to those employed for THF is attributed to the different physical properties exhibited by the solvents and hence slightly different electroosmotic mobilities.[7]

To increase the volume of product synthesised, the reagent concentrations were increased by a factor of 10; a standard solution of 1-phenylbutane-1,3-dione **10** (40 μL, 1.0 M) in THF was placed in reservoir A and a solution of hydrazine monohydrate **3** (40 μL, 1.0 M) in THF in reservoir B; the reaction products were collected in THF at reservoir C. The reagents were manipulated within the device using the following applied fields, 364, 341, and 0 V cm^{-1}, resulting in quantitative conversion of the 1,3-diketone **10** to 3-methyl-5-phenyl-1*H*-pyrazole, **5**. Using the same reaction conditions, the reaction was repeated in DMF, whereby 100% conversion to the pyrazole **5** was again obtained. The reaction was subsequently repeated using the diketones, 2-benzoylcyclo-

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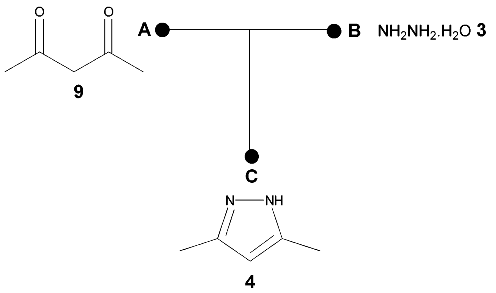


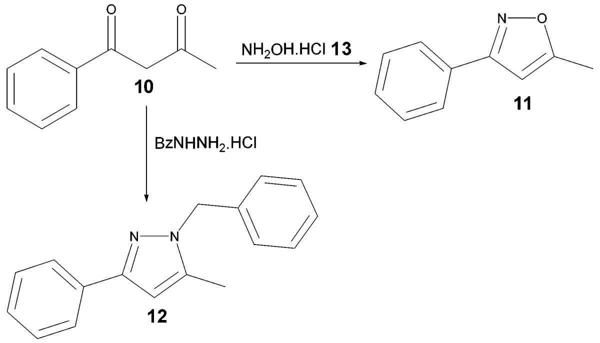
Figure 4. **Schematic of the microreactor used to synthesise 1,2-azoles.**

Table 2. **Comparison of the conversions obtained for the preparation of 1,2-azoles 4−12 in batch and a microreactor**

	conversion/%		
product no.	batch	microreactor	applied field/V cm^{-1}
4	62	100[a] (100)[a]	292, 318, and 0
5	63	100[a] (100)[a]	364, 341, and 0
6	72	100[a]	260, 303, and 0
7	64	100[a]	386, 364, and 0
8	71	98[a]	409, 386, and 0
11	52	98[a]	292, 318, and 0
12	76	42[a] (100)[c]	364, 341, and 0

[a] Reaction performed using THF. [b] Reaction performed using DMF. [c] Reaction performed using stopped flow regime.

Scheme 2. **Preparation of an isoxazole 11 and a substituted pyrazole 12**



hexanone, 1,3-diphenylpropane-1,3-dione, and 2-methyl-1-phenylbutane-1,3-dione to afford 3-phenyl-4,5,6,7-tetrahydro-2*H*-indazole **6**, 3,5-diphenyl-1*H*-pyrazole **7**, and 3,4-dimethyl-5-phenyl-1*H*-pyrazole **8** in 100, 100, and 98% conversion respectively (Table 2).

Having successfully demonstrated the preparation of an array of pyrazoles, the technique was extended to the synthesis of an isoxazole **11** and a substituted pyrazole **12** (Scheme 2). A standard solution of 1-phenylbutane-1,3-dione **10** (40 μL, 1.0 M) in THF was placed in reservoir A and a solution of hydroxylamine hydrochloride **13** (40 μL, 1.0 M) in THF in reservoir B, and the reaction products were collected in reservoir C. Manipulation of the reagents using the following applied fields, 296, 409, and 0 V cm^{-1} resulted in 98% conversion to 5-methyl-3-phenylisoxazole **11**.

Using the following procedure, the substituted pyrazole, 1-benzyl-3-methyl-5-phenyl-1*H*-pyrazole **12**, was synthesised within a microreactor. A standard solution of phenylbutane-1,3-dione **10** (40 μL, 1.0 M) in THF was placed in reservoir A and a solution of benzyl hydrazine hydrochloride **14** (40 μL, 1.0 M) in THF in reservoir B, and the reaction products were collected in reservoir C. Manipulation of the reagents using the following applied fields, 318, 318, and 0 V cm^{-1} resulted in 42% conversion to pyrazole **12**. This was later increased to 100% by employing a stopped-flow regime. The technique involved the application of a field for 2.5 s and no field for 5.0 s; these steps were subsequently repeated over a period of 20 min and served to increase the reagents' residence time within the device (Table 2).[8]

As Table 2 illustrates, compared to traditional batch techniques, the use of a microreactor is advantageous because not only are excellent conversions obtained in all cases, but the reaction times involved are also decreased from typically hours to seconds.

Since conducting this investigation, Garcia-Egido et al.[9] demonstrated the preparation of a pyrazole library (21 compounds) within a pressure-driven system. The authors employed a serpentine reactor, with channel dimensions in the range of 100 μm × 25 μm × 3 m, coupled to an LC−UV−MS. To prepare an array of compounds, 2.5 μL slugs of reagent were introduced into the device at 1 μL min^{-1} and mobilised throughout the channel network using methanol as the driving solvent. Using 0.01 M diketone and 0.8 M hydrazine monohydrate **3** solutions and a residence time of 210 s enabled the sequential preparation of a range of pyrazoles in moderate to high conversion (35−99%). However, compared to the system discussed herein, the pressure-driven approach is disadvantageous as the device is relatively large (6 × 2.5 cm), the reaction requires a lengthy equilibration time (10 min) to ensure stable flow, and the reactions are performed using 81 equiv of hydrazine monohydrate **3**. Although the quantities of reagents employed are reduced due to the desire to prepare small quantities of each compound, the use of an 81-fold excess of hydrazine monohydrate **3** is unnecessary with respect to both product purification and environmental concerns, i.e., disposal.

Using the preparation of 5-methyl-3-phenylisoxazole **11** as a model and employing 1.0 M standard solutions, the EOF-based device can synthesise 0.339 g day^{-1} (based on 98% conversion and an average flow rate of 1.5 μL min^{-1}). Therefore, if 1000 microreactors were operated in parallel, 339.0 g day^{-1} could be synthesised, compared to the pressure-driven system whereby 2.5 × 10^{-6} g of product is prepared per 2.5 μL aliquot injected. Therefore, if only a small amount of compound is required for biological evaluation, devices of the kind used by Garcia-Egido et al.[9] can be employed as a means of preparing a large number of samples, i.e., libraries, in a short period of time. Alternatively the approach of scale-out can be employed as a means of preparing fine chemicals or pharmaceuticals on a large-scale, demonstrating the flexibility associated with microreaction technology.

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Summary

In conclusion, we have demonstrated a simple, stoichiometric technique for the preparation of an array of 1,2-azoles within an EOF-based microreactor, whereby excellent conversions were obtained in all cases.

Experimental Section

Materials and Methods. All materials (analytical grade) were purchased from Aldrich and were used without purification. All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Joel GX400 spectrometer and the chemical shifts given in parts per million (ppm) with coupling constants in Hertz (Hz). The following abbreviations are used to report NMR data: s = singlet, d = doublet, t = triplet, br s = broad singlet, m = multiplet, and C_0 = quaternary carbon. Gas chromatography−mass spectrometry (GC−MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex) and ultrahigh purity helium (99.999%, Energas) carrier gas. Samples were analysed using the following method: injector temperature 200 °C, helium flow rate 1 mL min^{-1}, oven temperature 50 °C for 4 min and then ramped to 250 °C at 30 °C min^{-1}, with a 3.0 min filament delay.

Microreactor Methodology. The reactions described herein were carried out using a three-channel microreactor, as illustrated in Figure 1, with channel dimensions of 350 μm (wide) × 52 μm (deep) × 2.5 cm (long).[10] To minimise the effect of pressure gradients within the microchannels, microporous silica frits were placed within the channels.[11] To mobilise reagents by EOF, platinum electrodes (0.5 mm o.d. × 2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high-voltage power supply (HVPS) (capable of applying 0−1000 V to four pairs of outputs) (Kingfield Electronics). Automation of the HVPS using an in-house LabVIEW program enabled complex sequences of voltages to be investigated. To enable the results obtained to be applied to devices of different dimensions, voltages are reported as applied fields (V cm^{-1}), i.e. voltage/channel length. To monitor the progress of the reaction, experiments were conducted over a period of 20 min, after which the product reservoir was analysed by GC−MS, whereby comparison of the amount of product with respect to residual starting material enabled the progression of the reaction to be determined.

General Procedure for the Preparation of 1,2-Azoles in Batch. A typical experimental procedure was as follows: Hydrazine monohydrate **3** (1.1 equiv) in THF (2 mL $mmol^{-1}$) was added via a syringe to a stirred solution of 1,3-diketone in THF (2 mL $mmol^{-1}$) over a period of 30 min. After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of water (50 mL), and the reaction products were extracted into ethyl acetate (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, whereby purification by silica gel chromatography (7−10% ethyl acetate in hexane) afforded the respective 1,2-azole.

3,5-Dimethyl-1*H*-pyrazole (4):[12] (0.48 g, 100%) as a pale yellow solid; δ_H (400 MHz, $CDCl_3$/TMS) 2.19 (6H, s, 2 × CH_3), 5.75 (1H, s, CH), and 7.25 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$/TMS) 12.2 (2 × CH_3), 104.0 (CH), and 144.4 (2 × CN); *m/z* (EI) 97 (M^+ + 1, 100%) and 96 (5); GC−MS retention time R_T = 7.35 min.

3-Methyl-5-phenyl-1*H*-pyrazole (5):[13] (0.49 g, 100%) as a pale yellow solid; δ_H (400 MHz, $CDCl_3$/TMS) 2.35 (3H, s, CH_3), 6.36 (1H, s, CH), and 7.29−7.62 (5H, m, Ar) (NH not observed); δ_C (100 MHz, $CDCl_3$/TMS) 11.8 (CH_3), 102.2 (CH), 125.7 (CH), 127.0 (2 × CH), 128.0 (CH), 128.6 (CH), 132.3 (C_0), 143.2 (*C*NCH_3), and 149.9 (CN); *m/z* (EI) 159 (M^+ + 1, 75%), 158 (100), and 77 (5); GC−MS retention time R_T = 10.43 min.

3-Phenyl-4,5,6,7-tetrahydro-2*H*-indazole (6):[14] (0.49 g, 94%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$/TMS) 1.85 (4H, m, 2 × CH_2), 2.74 (2H, t, *J* 5.7, CH_2), 2.86 (2H, t, *J* 5.7, CH_2), 7.46 (3H, m, Ar), 7.80 (2H, m, Ar), and 12.14 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$/TMS) 21.4 (3 × CH_2), 22.7 (CH_2), 114.4 (C_0), 127.5 (C_0), 127.6 (2 × CH), 129.2 (2 × CH), 129.9 (CH), 142.4 (CN), and 145.4 (CN); *m/z* (EI) 199 (M^+ + 1, 100%), 198 (5), and 170 (10); GC−MS retention time R_T = 12.71 min.

3,5-Diphenyl-1*H*-pyrazole (7):[13] (0.42 g, 86%) as a pale yellow solid; δ_H (400 MHz, $CDCl_3$/TMS) 7.13 (1H, s, CH), 7.49 (6H, m, Ar), 7.96 (4H, m, Ar), and 9.96 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$/TMS) 100.2 (CH), 126.0 (4 × CH), 127.6 (2 × C_0), 128.6 (4 × CH), 129.3 (2 × CH), and 147.0 (2 × CN); *m/z* (EI) 221 (M^+ + 1, 20%), 220 (100), and 77 (25); GC−MS retention time R_T = 14.98 min.

3,4-Dimethyl-5-phenyl-1*H*-pyrazole (8):[15] (0.45 g, 93%) as a pale yellow solid; δ_H (400 MHz, $CDCl_3$/TMS) 2.13 (3H, s, CH_3), 2.25 (3H, s, CH_3), 7.22 (3H, m, Ar), 7.32 (2H, m, Ar), and 18.29 (1H, s, NH); δ_C (100 MHz, $CDCl_3$/TMS) 10.9 (CH_3), 31.4 (CH_3), 127.4 (2 × CH), 127.9 (2 × CH), 128.7 (CH), 130.9 (C_0), 141.9 (CNCH_3), and 146.8 (CN); *m/z* (EI) 173 (M^+ + 1, 70%), 172 (100), and 77 (15); GC−MS retention time R_T = 10.72 min.

5-Methyl-3-phenylisoxazole (11).[16] Hydroxylamine hydrochloride **13** (0.21 g, 3.09 mmol) was dissolved in THF (10 mL) and added dropwise to a stirred solution of 1-phenylbutane-1,3-dione **10** (0.50 g, 3.09 mmol) in THF (10 mL). After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of water (50 mL), and the reaction products were extracted into ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by silica gel chromatography. Elution with 10% ethyl acetate in hexane

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afforded 5-methyl-3-phenylisoxazole **11** (0.46 g, 93%) as a pale yellow solid; δ_H (400 MHz, $CDCl_3$/TMS) 2.34 (3H, s, CH_3), 6.35 (1H, s, CH), 7.42 (3H, m, Ar), and 7.74 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 11.5 (CH_3), 100.2 (CH), 125.7 (2 × CH), 127.6 (C_0), 128.9 (2 × CH), 130.0 (CH), 160.34 (CN), and 169.6 (CO); *m*/*z* (EI) 160 ($M^+ + 1$, 30%), 159 (100), 105 (50), and 77 (10); GC−MS retention time, $R_T = 9.56$ min.

1-Benzyl-3-methyl-5-phenyl-1*H*-pyrazole (12).[17] Benzyl hydrazine hydrochloride **14** (0.61 g, 3.09 mmol) was dissolved in THF (10 mL) and added dropwise to a stirred solution of 1-phenylbutane-1,3-dione **10** (0.50 g, 3.09 mmol) in THF (10 mL). After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of water (50 mL), and the reaction products were extracted into ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and subsequently purified by silica gel chromatography. Elution with 7% ethyl acetate in hexane afforded 1-benzyl-3-methyl-5-phenyl-1*H*-pyrazole **12** (0.74 g, 97%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$/TMS) 2.34 (3H, s, CH_3), 5.28 (2H, s, CH_2), 6.14 (1H, s, CH), 7.03 (2H, m, Ar), and 7.22−7.38 (8H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 13.7 (CH_3), 52.2 (CH_2), 106.2 (CH), 126.7 (2 × CH), 127.1 (CH), 127.8 (4 × CH), 128.2 (3 x CH), 130.9 (C_0), 132.4 (C_0), 145.0 (CN), and 148.4 (CN); *m*/*z* (EI) 249 ($M^+ + 1$, 100%), 248 (20), 91 (15), and 77 (10); GC−MS retention time, $R_T = 12.02$ min.

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Acknowledgment

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